REMARKS

Claims 1-6 currently appear in this application. The Office Action of February 25, 2002, has been carefully studied. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicants respectfully request favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

Trademarks

The trademarks ENBREL and REMICADE have now been fully capitalized wherever they appear in the application. In each instance, the trademarks are accompanied by the generic terminology.

Rejections under 35 U.S.C. 112

Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleges that it is not clear what is encompassed by "a compound that neutralizes the effect of secreted TNF alpha."

This rejection is respectfully traversed. It is clear from the specification, particularly at page 4, paragraph 15, that the present invention is directed to

treating hepatitis by administering a compound that neutralizes the activity of secreted TNF, such as a ligand binding protein of the human p75 TNF receptor linked to the Fc portion of human IgG1, or a humanized monoclonal antibody that neutralizes the activity of TNF. These compounds have been found to reverse evidence of hepatic inflammation associated with active hepatitis. As it is the TNF alpha that causes the inflammation, it is clear that compounds that neutralize the effects of TNF alpha are compounds which are encompassed by the present invention. What is important in the present invention is to neutralize the effects of secreted TNF alpha; the mechanisms by which this is accomplished is immaterial.

Submitted herewith are copies of information about infliximab and etanercept, which both of which characterize these compounds as "anti-TNF" or "TNF inhibitors."

Claims 3 and 4 are said to be indefinite in reciting p75:FC inhibitor", as the Examiner states that it is not clear whether p75:FC inhibitor" is a type of inhibitor or is that which is to be inhibited.

This rejection is respectfully traversed. As stated in the specification as filed at page 4, last sentence of paragraph 0014, the compounds which are

useful in the present invention are those which neutralize the effects of secreted TNF by inhibiting p75:FC. That is, the compounds inhibit p75:FC.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains.

This rejection is respectfully traversed. The Examiner has given no reason that one skilled in the art could not extrapolate from the results with one patient that administration of an anti-TNF alpha compound would improve viral levels in patients suffering from hepatitis. The fact that Campbell et al. successfully treated a patient suffering from hepatitis with inflximab, another anti-TNF alpha compound, provides additional evidence that anti-TNF alpha compounds are useful in treating hepatitis. The present inventors have discovered that inhibiting TNF alpha reverses the evidence of hepatic inflammation associated with active hepatitis.

As the Examiner is well aware, a specification which contains a teaching of the manner and process of making and using an invention in terms which correspond to the scope of those used in describing and defining the subject matter sought to be patented must be taken as

being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support (MEPE Section 2164.04). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue, *In re Angstadt*, 190 USPQ 219 (CCPA 1976). While no examples are required, the present application provides an example of successful human treatment, and one skilled in the art can certainly appreciate that administration of a compound which neutralizes the effects of secreted TNF-alpha can be used to treat hepatitis.

Art Rejections

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by The Merck Manual of Diagnosis and Therapy. The Examiner states that the Merck Manual discloses treatment of autoimmune hepatitis with corticosteroids and treatment of hepatitis B and hepatitis C with interferon alpha, and discloses that both treatments result in reduction of inflammation.

This rejection is respectfully traversed. There is nothing at all in the Merck Manual that discloses or suggests that anti-TNF alpha compounds should be used in treating hepatitis. In fact,

corticosteroids are said to be **contraindicated**, and interferon-alpha is said to suppress viral replication, even though interferon-alpha **initially** suppresses inflammation in about 50% of patients. One skilled in the art, reading this, would certainly not be led to treat patients with hepatitis with an anti-TNF alpha compound, as there is nothing in the Merck Manual that suggests using any such compound.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

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"Version with markings to show changes"

Page 2, please amend paragraph [0006] as follows:

[0006] There are currently two drugs which have been approved for treatment of rheumatoid arthritis that act by neutralizing the activity of secreted TNF: etanercept (~~Enbrel~~**ENBREL**), which is based on a p75:pC receptor and a humanized monoclonal antibody that neutralizes the activity of TNF, such as inflixamab (~~Remicade~~**REMICADE**). Etanercept, or ~~Enbrel~~**ENBREL**, is an extracellular ligand binding protein of the human p75 TNF receptor (TNF-R) linked to the Fc portion of human IgG1. Infliximab, or ~~Remicade~~**REMICADE**, is a humanized monoclonal antibody that neutralizes the activity of secreted TNF. Both ~~Enbrel~~ **ENBREL (Etanercept)** and ~~Remicade~~ **REMICADE (Infliximab)** potently bind TNF and block inflammation by inhibiting the downstream effect of this cytokine. ~~Enbrel~~ **ENBREL (Etanercept)** can bind to lymphotoxin alpha as well as to TNF.

Page 3, please amend paragraph [0009] as follows:

[0009] ~~Enbrel~~ **ENBREL (Etanercept)** has been reported to have several side effects, which include possible exacerbation of bacterial infections, including sepsis.

Page 4, please amend paragraph [0014] as follows:

[0014] According to the present invention, compounds that neutralize the effects of secreted TNF not only eliminate the symptoms of rheumatoid arthritis, but also reverse the clinical symptoms associated with hepatitis. Thus, the present invention includes treating a patient suffering from hepatitis with a compound that neutralizes the effects of secreted TNF by inhibiting p75:FC, such as ~~Enbrel~~ **ENBREL (Etanercept)** or ~~Remicade~~**REMICADE (Infliximab)**.

Page 4, please amend paragraph [0016] as follows:

[0016] A patient was identified with typical symptoms of rheumatoid arthritis, including polyarticular joint swelling and pain. The patient also had evidence of active hepatitis, which was characterized by chronic and persistent elevations of hepatic transaminases (AST, ALT) as well as a marked elevation of serum hepatitis C viral RNA. The patient was treated with various DMARs and NSAIDS for a period of three years, and showed very little signs of relief from rheumatoid arthritis. The patent was then selected for treatment with ~~Enbrel~~ **ENBREL (Etanercept)** at 25 mg. twice weekly.

Page 5, please amend paragraph [0018] as follows:

[0018] The patient was administered 25 mg. of ~~Enbrel~~**ENBREL (Etanercept)**, an extracellular ligand binding protein of the human p75 TNF receptor linked to the Fc portion of human IgG1, twice weekly for five weeks. After five weeks of treatment with **ENBREL (Etanercept)** ~~Enbrel~~, the rheumatoid arthritis showed 20-30% symptomatic improvement. The hepatitis symptoms after treatment included viral RNA of 165,000 units and a normalization of liver enzymes, including aspartate transaminase and alanine transaminase, on repeated testing after five weeks of treatment with **ENBREL (Etanercept)** ~~Enbrel~~.